Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Specific Issues in Antiretroviral Therapy for HIV-Infected Adolescents (Updated August 11, 2011)

Panel's Recommendations
• Antiretroviral therapy (ART) regimens must be individually tailored to the adolescent. Adolescents with perinatal infection generally have a very different clinical course and treatment history than those who acquired HIV during adolescence **(AIII)**.
• Appropriate dosing of antiretroviral (ARV) medications for adolescents is complex, not always predictable, and dependent upon multiple factors, including body mass and composition and physiologic development **(AII)**.
• Effective and appropriate contraceptive methods for adolescence should be selected to reduce the likelihood of unintended pregnancy and to prevent transmission of HIV to sexual partners **(AI)**.
• Providers should be aware of potential interactions between ARV drugs and hormonal contraceptives, which could lower contraceptive efficacy **(AII*)**.
• Efavirenz should not be used by an adolescent female who desires to become pregnant or who does not use effective and consistent contraception **(AII)**. Efavirenz also should not be used throughout the first trimester of pregnancy **(AII)**.
• Pediatric and adolescent care providers should prepare adolescent patients for the transition into adult care settings **(AIII)**.

Background

An increasing number of HIV-infected children who acquired HIV infection through perinatal transmission are now surviving into adolescence. They generally have had a long clinical course and extensive ARV treatment history[1]. Adolescents with behaviorally acquired infection (i.e., infection acquired via sexual activity or intravenous substance use) generally follow a clinical course similar to that in adults. Because behaviorally infected adolescents are at an early stage of HIV infection, they are potential candidates for early intervention and treatment[2].

Dosing of Antiretroviral Therapy for HIV-Infected Adolescents

Puberty is a time of somatic growth and sexual maturation, with females developing more body fat and males more muscle mass. These physiologic changes may affect drug pharmacokinetics (PKs), which is especially important for drugs with a narrow therapeutic index that are used in combination with protein-bound medicines or hepatic enzyme inducers or inhibitors[3]. Dosages of medications for HIV infection and opportunistic infections (OIs) traditionally have been prescribed according to Tanner staging of puberty[4] rather than strictly on the basis of age[2]. Using the Tanner method, adolescents in early puberty (Tanner Stages 1 and 2) are administered doses using pediatric schedules, whereas those in late puberty (Tanner Stage 5) are administered doses using adult schedules. However, Tanner stage and age are not necessarily directly predictive of drug PKs. Puberty may be delayed in children who were infected with HIV perinatally[5], adding to discrepancies between Tanner stage-based dosing and age-based dosing, although delayed onset of puberty appears to be uncommon in children receiving potent combination therapy[6].

Many ARV medications (e.g., abacavir, emtricitabine, lamivudine, tenofovir, and some protease inhibitors [PIs]) are administered to children at higher weight- or surface area-based doses than would be predicted by direct scaling of adult doses, based upon reported PK data indicating more rapid drug clearance in children. Continued use of these pediatric weight- or surface area-based doses as a child grows during adolescence can result in medication doses that are higher than the usual adult doses. Data suggesting optimal doses for every ARV medication for adolescents are not available. Appendix A: Pediatric Antiretroviral Drug Information includes a discussion of data relevant to adolescents for individual drugs and notes the age listed on the drug label for adult dosing, when available. Many factors may affect the transition from pediatric to adult doses. In addition to toxicity, pill burden, adherence, and virologic and immunologic parameters, factors may include social determinants, such as housing, family support, employment, and recent discharge from the foster care system.

Adolescent Contraception, Pregnancy, and Antiretroviral Therapy

Adolescents with HIV infection, regardless of mode of acquisition, may be sexually active. Contraception methods and safer sex techniques for prevention of HIV transmission should be discussed with them regularly (see U.S. Medical Eligibility Criteria for Contraceptive Use)[7].

The possibility of planned or unplanned pregnancy should be considered when selecting an ARV regimen for the adolescent female. The most vulnerable period in fetal organogenesis is early in gestation, often before pregnancy is recognized. Sexual activity, reproductive plans including preconception care, and use of effective contraception should be discussed with the patient. In addition, concerns about specific ARV drugs and birth defects should be addressed immediately to preclude misinterpretations or lack of adherence for adolescents with unexpressed plans for pregnancy. Adolescent females who are trying to conceive or who are not using effective and consistent contraception should avoid efavirenz-containing regimens because of the potential for teratogenicity with fetal exposure to efavirenz in the first trimester.

Contraceptive-Antiretroviral Drug Interactions

Several PI and non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs interact with oral contraceptives, resulting in possible decreases in ethinyl estradiol or increases in estradiol or norethindrone levels (see the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents available at http://aidsinfo.nih.gov)[8]. These changes may decrease the effectiveness of the oral contraceptives or potentially increase the risk of estrogen- or progestin-related side effects. Providers should be aware of these drug interactions and consider alternative or additional contraceptive methods for patients receiving ARV drugs with such interactions. Whether interactions with ARV drugs would compromise the contraceptive effectiveness of progestogen-only injectable contraceptives (such as depot methoxyprogesterone acetate [DMPA]) is unknown because these methods produce higher blood hormone levels than other progestogen-only oral contraceptives and combined oral contraceptives. In one study, the efficacy of DMPA was not altered among women receiving concomitant nelfinavir-, efavirenz-, or nevirapine-based treatment, with no evidence of ovulation during concomitant administration for 3 months, no additional side effects, and no clinically significant changes in ARV drug levels[9-10]. At this time concerns about bone mineral loss with long-term use of DMPA with or without ART (specifically tenofovir)[11] should not preclude use of DMPA as an effective contraceptive. However, more diligent monitoring of bone mineral density (BMD) in young women on DMPA may need to be considered[11]. Minimal information exists about drug interactions with use of newer hormonal contraceptive methods (e.g., patch, vaginal ring). Intrauterine device (IUD) use while on ART is not restricted by current guidelines; however, IUD users with AIDS

should be closely monitored for pelvic infection[7]. Adolescents who desire to become pregnant should be referred for preconception counseling and care, including discussion of special considerations with ART use during pregnancy (see Health and Human Services [HHS] Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health *and* Interventions to Reduce Perinatal HIV Transmission in the United States available at http://aidsinfo.nih.gov)[12].

HIV-Infected Pregnant Adolescents and Outcomes

Pregnancy should not preclude the use of optimal therapeutic regimens. However, because of considerations related to prevention of perinatal transmission and to maternal and fetal safety, timing of initiation of treatment and selection of regimens may be different for pregnant women than for nonpregnant adults or adolescents. Details regarding choice of ARV regimen in pregnant HIV-infected women, including adolescents, are provided in HHS Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health *and* Interventions to Reduce Perinatal HIV Transmission in the United States available at http://aidsinfo.nih.gov[12]. Although information about the pregnancies of adolescents who were infected with HIV perinatally is limited, outcomes in this population appear similar to outcomes in adult cohorts[13-16].

Transition of Adolescents into Adult HIV Care Settings

Facilitating a smooth transition of adolescents with chronic health conditions from their pediatric/adolescent medical home to adult care can be difficult and is especially challenging for adolescents infected with HIV. Transition is described as "a multifaceted, active process that attends to the medical, psychosocial, and educational or vocational needs of adolescents as they move from the child-focused to the adult-focused health-care system"[17]. Care models for children and adolescents with perinatally acquired HIV tend to be family centered, consisting of a multidisciplinary team that often includes pediatric or adolescent physicians, nurses, social workers, and mental health professionals. These providers generally have long-standing relationships with patients and their families, and care is rendered in discreet, more intimate settings. Although expert care is also provided under the adult HIV care medical model, the adolescent may be unfamiliar with the more individual-centered, busier clinics typical of adult medical providers and uncomfortable with providers who often do not have a long-standing relationship with the adolescent. Providing the adolescent and the adult medical care provider with support and guidance regarding expectations for each partner in the patient-provider relationship may be helpful. In this situation, it may also be helpful for the pediatric and adult provider to share joint care of the patient for a period of time. Providers should also have a candid discussion with the transitioning adolescent to understand what qualities the adolescent considers most important in a provider (e.g., confidentiality, small clinic size, after-school appointments). Pediatric and adolescent providers should have a formal plan to transition adolescents to adult care. Some general guidelines about transitional plans and who might best benefit from them are available[18-20].

References

1. Van Dyke RB, Patel K, Siberry GK, et al. Antiretroviral Treatment of U.S. Children with Perinatally-Acquired HIV Infection: Temporal Changes in Therapy between 1991 and 2009 and Predictors of Immunologic and Virologic Outcomes. *J Acquir Immune Defic Syndr.* 2011;57(2):165-173.
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. 2011:1-166.

3. Rogers A. Pharmacokinetics and pharmacodynamics in adolescents. January 20-21, 1994. Proceedings. *J Adolesc Health.* 1994;15(8):605-678.
4. Schneider MB. Physical examination. In: Friedman SB, Fisher MM, Schoenberg SK, Alderman EM, eds. Comprehensive adolescent health care. 2nd ed. St. Louis, MO: Mosby-Year Book, Inc.1998:69-80.
5. Buchacz K, Rogol AD, Lindsey JC, et al. Delayed onset of pubertal development in children and adolescents with perinatally acquired HIV infection. *J Acquir Immune Defic Syndr.* 2003;33(1):56-65.
6. del Bianco GP, Heresi G, Frederick T, et al. for the LEGACY Consortium. Onset of puberty and Sexual Maturation in Perinatally HIV-infected Children and Adolescents in the United States in the HAART era. Abstract presented at 48th Annual IDSA Meeting, Vancouver, October 21-24, 2010. 2010.
7. Farr S, Folger SG, Paulen M, et al. U S. Medical Eligibility Criteria for Contraceptive Use, 2010: adapted from the World Health Organization Medical Eligibility Criteria for Contraceptive Use, 4th edition. *MMWR Recomm Rep.* 2010;59(RR-4):1-86.
8. El-Ibiary SY, Cocohoba JM. Effects of HIV antiretrovirals on the pharmacokinetics of hormonal contraceptives. *Eur J Contracept Reprod Health Care.* 2008;13(2):123-132.
9. Watts DH, Park JG, Cohn SE, et al. Safety and tolerability of depot medroxyprogesterone acetate among HIV-infected women on antiretroviral therapy: ACTG A5093. *Contraception.* 2008;77(2):84-90.
10. Cohn SE, Park JG, Watts DH, et al. Depo-medroxyprogesterone in women on antiretroviral therapy: effective contraception and lack of clinically significant interactions. *Clin Pharmacol Ther.* 2007;81(2):222-227.
11. Beksinska ME, Smit JA, Ramkissoon A. Progestogen-only injectable hormonal contraceptive use should be considered in analysis of studies addressing the loss of bone mineral density in HIV-positive women. *J Acquir Immune Defic Syndr.* 2010;54(4):e5.
12. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health *and* Interventions to Reduce Perinatal HIV Transmission in the United States. May 24, 2010:1-117. http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf.
13. Cruz ML, Cardoso CA, Joao EC, et al. Pregnancy in HIV vertically infected adolescents and young women: a new generation of HIV-exposed infants. *AIDS.* 2010; 24(17):2727-2731.
14. Elgalib A, Hegazi A, Samarawickrama A, et al. Pregnancy in HIV-infected teenagers in London. *HIV Med.* 2011;12(2):118-123.
15. Meloni A, Tuveri M, Floridia M, et al. Pregnancy care in two adolescents perinatally infected with HIV. *AIDS Care.* 2009;21(6):796-798.
16. Williams SF, Keane-Tarchichi MH, Bettica L, et al. Pregnancy outcomes in young women with perinatally acquired human immunodeficiency virus-1. *Am J Obstet Gynecol.* 2009;200(2):e1-5.
17. Reiss JG, Gibson RW, Walker LR. Health care transition: youth, family, and provider perspectives. *Pediatrics.* 2005;115(1):112-120.
18. American Academy of Pediatrics, American Academy of Family Physicians, American College of Physicians-American Society of Internal Medicine. A consensus statement on health care transitions for young adults with special health care needs. *Pediatrics.* 2002;110(6 Pt 2):1304-1306.
19. Rosen DS, Blum RW, Britto M, et al. Transition to adult health care for adolescents and young adults with chronic conditions: position paper of the Society for Adolescent Medicine. *J Adolesc Health.* 2003;33(4):309-311.
20. Gilliam PP, Ellen JM, Leonard L, et al. Transition of Adolescents With HIV to Adult Care: Characteristics and Current Practices of the Adolescent Trials Network for HIV/AIDS Interventions. *J Assoc Nurses AIDS Care.* 2011;22(4):283-294.